Phase II Study of Atezolizumab + FLOT vs. FLOT Alone in Patients With Gastric Cancer and GEJ (DANTE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest

Information provided by (Responsible Party):
IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest

Study Description
Brief Summary:
This is a multicenter, randomized, controlled, open-label study comparing perioperative atezolizumab with FLOT chemotherapy versus FLOT alone in patients with locally advanced, operable adenocarcinoma of the stomach or
The study will evaluate the safety and efficacy of the study treatment regimens. The study includes an evaluation of rate of immune cell infiltration into the esophagogastric tumor tissue following two and four cycles of neoadjuvant therapy. Potential study participants will be assessed for eligibility during a 28-day screening period that includes central verification of clinical stage and eligibility. Eligible patients will be enrolled and randomized to perioperative treatment with either atezolizumab with FLOT (Arm A) or FLOT alone (Arm B). Randomization will occur in a 1:1 ratio with stratification by clinical nodal stage (N+ vs. N-), location of the primary (GEJ type I vs. GEJ type II/III vs. stomach), and MSI-status (MSI / MMRd vs. MSS / MMRp). Quantitative PDL-1 mRNA expression will be performed but not used as stratification factor.

Following randomization, study patients will enter the study treatment period which will last approximately 22 to 52 weeks depending on treatment arm and timing of surgery.

Arm A: FLOT with Atezolizumab:
Patients randomized to treatment Arm A will receive atezolizumab + FLOT in four 2-week treatment cycles as described below prior to undergoing surgery. Following surgery, patients will receive four further 2-week cycles of atezolizumab + FLOT followed by 8 additional 3-week treatment cycles with atezolizumab alone.

Arm B: FLOT alone:
Patients randomized to Arm B will receive FLOT alone for four 2-week treatment cycles prior to surgery. Following surgery, patients will receive four further 2-week cycles of chemotherapy alone.
Experimental: Arm A: FLOT with Atezolizumab

Patients randomized to treatment Arm A will receive atezolizumab (840 mg IV over 1 hour) + FLOT in four 2-week treatment cycles prior to undergoing surgery. Following surgery, patients will receive four further 2-week cycles of atezolizumab + FLOT followed by 8 additional 3-week treatment cycles with atezolizumab alone (maintenance setting: 1,200 mg q3w). FLOT can be deescalated to FLO, FLT or FL in case of chemorelated toxicity at any time and at the discretion of investigator.

Drug: Atezolizumab

Day 1 q2w: 840 mg IV over 1 hour (4 cycles perioperative with FLOT) + Day 1 q3w: 1200 mg IV over 1 hour (8 additional cycles monotherapy)

Other Name: TECENTRIQ

Drug: 5-Fluorouracil

Day 1 q2w: 2600 mg/m² IV over 24 hours

Other Name: 5-FU

Drug: Calciumfolinat

Day 1 q2w: 200 mg/m² IV over 1 hour

Other Name: Leucovorin

Drug: Oxaliplatin

Day 1 q2w: 85 mg/m² IV over 2 hours

Other Name: ELOXATIN

Drug: Docetaxel

Day 1 q2w: 50 mg/m² IV over 1 hour

Other Name: TAXOTERE

Active Comparator: Arm B: FLOT alone

Patients randomized to Arm B will receive FLOT

Drug: 5-Fluorouracil

Day 1 q2w: 2600 mg/m² IV over 24 hours
alone for four 2-week treatment cycles prior to surgery. Following surgery, patients will receive four further 2-week cycles of chemotherapy alone. FLOT can be deescalated to FLO, FLT or FL in case of chemo-related toxicity at any time and at the discretion of investigator. Docetaxel 50 mg/m², d1 Oxaliplatin 85 mg/m², d1 Calciumfolinat 200 mg/m², d1 5-Fluorouracil 2600 mg/m², d1

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**Outcome Measures**

**Primary Outcome Measures**:

1. Comparison of DFS/PFS between arms [ Time Frame: 5 years ]

   to compare PFS/DFS in patients with locally advanced, operable esophagogastric adenocarcinoma receiving perioperative FLOT with atezolizumab versus FLOT alone in the intent to treat population (ITT) and where PFS/DFS is defined as the time from randomization to disease progression or relapse after surgery or death from any cause.

**Secondary Outcome Measures**:

1. Pathological complete regression (pCR, TRG 1a by Becker) rate [ Time Frame: after 4 cycles (each cycle is 14 days) + surgery; i.e. after 12 weeks in total ]

   Pathological complete regression (pCR, TRG 1a by Becker) rate where pCR is defined as the absence of residual tumor based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist.

2. Pathological complete and subtotal regression (TRG1a/b by Becker) [ Time Frame: after 4 cycles (each cycle is 14 days) + surgery; i.e. after 12 weeks in total ]

   Pathological complete and subtotal regression (TRG1a/b by Becker). TRG1a/b is defined as < 10% residual tumor per tumor bed based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist.

3. TRG1a and TRG1a/b in the sampled regional lymph nodes [ Time Frame: after 4 cycles (each cycle is 14 days) + surgery; i.e. after 12 weeks in total ]
TRG1a and TRG1a/b in the sampled regional lymph nodes.

4. R0 resection rate [Time Frame: after 4 cycles (each cycle is 14 days) + surgery; i.e. after 12 weeks in total]

R0 resection rate where R0 resection is defined as a microscopically margin negative resection with no gross or microscopic tumor remains in the areas of the primary tumor and/or sampled regional lymph nodes based on evaluation by the local pathologist.

5. Overall survival (OS) [Time Frame: 5 years]

Overall survival (OS) where OS is defined as the time from randomization to death from any cause.

6. Immune cell infiltration rate [Time Frame: at baseline, after 2 and after 4 cycles (each cycle is 14 days) of study treatment]

The immune cell infiltration rate determined by comparing the density of CD8-positive cells in tumor biopsies obtained from the same tumor location at baseline and after two and four cycles of study treatment.

Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Have provided written informed consent
2. In the investigator's judgement, is willing and able to comply with the study protocol including the planned surgical treatment
3. Female and male patients* ≥ 18 years of age
4. Diagnosed with histologically confirmed adenocarcinoma of the GEJ (Type I-III) or the stomach (cT2, cT3, cT4, any N category, M0), or (any T, N+, M0) that:
   a. is not infiltrating any adjacent organs or structures by CT or MRI evaluation
   b. does not involve peritoneal carcinomatosis
   c. is considered medically and technically resectable

Note: the absence of distant metastases must be confirmed by CT or MRI of the thorax and abdomen, and, if there is clinical suspicion of osseous lesions, a bone scan. If peritoneal carcinomatosis is suspected clinically, its absence must be confirmed by laparoscopy. Diagnostic laparoscopy is mandatory in patients with T3 or T4 tumors of the diffuse type histology in the stomach or upon request of the central review.

5. No prior cytotoxic or targeted therapy

6. No prior partial or complete esophagogastric tumor resection

7. ECOG \(\leq 1\)

8. Availability of a representative tumor specimen that is suitable for determination of PD-L1 and MSI status; MSI assessment will be performed locally or centrally and result must be available prior to randomization (for details, see chapter 9). PD-L1 will be assessed centrally but is not used for enrolment of the patients. The analysis requires paraffin embedded biopsy samples of the tumor.

9. Females of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (has not had \(\geq 12\) continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

10. Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

   a. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of 1% per year during the treatment period and for at least 3 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Men with a pregnant partner must agree to remain abstinent or to use a condom for the duration of the pregnancy.
11. Adequate hematological, hepatic and renal function as indicated by the following parameters:

- Leukocytes ≥ 3,000/mm³, platelets ≥ 100,000/mm³ without transfusion, absolute neutrophil count (ANC) ≥ 1500/mm³ without granulocyte colony-stimulating factor support, Hemoglobin ≥ 90 g/L (9 g/dL) - Patients may be transfused to meet this criterion.
- Bilirubin ≤ 1.5 x upper limit of normal, aspartate transaminase and alanine transaminase ≤ 2.5 x upper limit of normal
- Serum creatinine ≤ 1.5 x upper limit of normal, or glomerular filtration rate > 45 ml/min (calculated using the Cockcroft-Gault formula)
- Serum albumin ≥ 25 g/L (2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN; for patients receiving therapeutic anticoagulation: stable anticoagulant regimen

*There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.

Exclusion Criteria:

1. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein; Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
2. Any known contraindication (including hypersensitivity) to docetaxel, 5-FU, leucovorin, or oxaliplatin.
3. Active or History of autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Note: History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone, or controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible based on consultation with the sponsor's medical monitor. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
   - Rash must cover < 10% of body surface area
   - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
   - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months
4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, idiopathic pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Note: History of radiation pneumonitis within the radiation field (fibrosis) is permitted.
6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to...
randomization) or hepatitis C Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction testing is negative for HCV ribonucleic acid (RNA).

8. Active tuberculosis

9. Uncontrolled tumor-related pain; Patients requiring pain medication must be on a stable regimen at study entry

10. Administration of a live, attenuated vaccine within four weeks prior to start of enrollment, or anticipation that such a live attenuated vaccine will be required during the study or within 5 months after the last dose of atezolizumab

11. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti-PD-1, or anti-PDL1 therapeutic antibodies

12. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within four weeks or five half-lives of the drug, whichever is longer, prior to study enrollment

13. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to study enrollment. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

14. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina.

15. Clinically significant valvular defect

16. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

17. Known central nervous system metastases

18. Peripheral polyneuropathy ≥ NCI CTCAE grade 2

19. Serum albumin < 2.5 g/dL.

20. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)

21. Serious infection requiring oral or IV antibiotics within 14 days prior to study enrollment

22. Chronic inflammatory bowel disease

23. Clinically significant active gastrointestinal bleeding

24. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment

25. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results

26. Participation in another interventional clinical study ≤ 30 days prior to study enrollment or planned participation in such a study at the same time as this study
27. Receipt of an investigational drug within 28 days prior to initiation of study drug
28. Pregnancy or breast feeding, or planning to become pregnant within 5 months after the end of treatment. Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

Contacts and Locations

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number):

NCT03421288

Contacts

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More Information

Responsible Party: IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest
ClinicalTrials.gov Identifier: NCT03421288
Other Study ID Numbers: DANTE/FLOT8
2017-001979-23 (EudraCT Number)
MO30039 (Other Identifier: Roche)
AIO-STO-0317 (Other Identifier: AIO number)
First Posted: February 5, 2018
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Last Verified: December 2018

Individual Participant Data (IPD) Sharing Statement:
Plan to Share IPD: No
Plan Description: No IPD will be shared.

Studies a U.S. FDA-regulated Drug Product: No
Studies a U.S. FDA-regulated Device Product: No
Product Manufactured in and Exported from the U.S.: No

Additional relevant MeSH terms:
Adenocarcinoma
Stomach Neoplasms
Carcinoma
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Neoplasms
Gastrointestinal Neoplasms
Digestive System Neoplasms
Neoplasms by Site
Digestive System Diseases
Gastrointestinal Diseases
Stomach Diseases
Docetaxel
Oxaliplatin
Fluorouracil
Atezolizumab
Antibodies, Monoclonal
Antineoplastic Agents
Tubulin Modulators
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Physiological Effects of Drugs

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